REMARKS

Objections and Requirements

Responsive to the Examiner's requirement for a corrective Oath or Declaration, the new declaration is in the process of being executed by the various inventors, and its submission will be addressed as soon as possible. A certified copy of the foreign priority UK application 0219459.5, filed August 21, 2002, is being filed concurrently herewith via Express Mail. In accordance with page 10, paragraph 22 of the Office Action, it is noted that parent PCT Appl. No. PCT/EP03/09056 published as WO 2004/018520 A1. Applicants respectfully request that the Examiner take all such priority filings and publications into account in reconsidering this application.

Objection to the Specification was made by the Examiner because of a blank space in the first paragraph, the form of trademark usage in paragraphs 0109 and 0112, and incorporation by reference to a non-patent literature reference in paragraph 0009. A substitute Specification, excluding the claims, is filed herewith along with a marked copy of the same to show changes. Paragraph number has been modified to correct a clerical error in the paragraph numbering at the transition from paragraph number 0099 to paragraph number 0100 in the original Specification. In addition, "Section 1.1" has been replaced by --- paragraphs 0088-0096 --- in the Specification, as this corrects a typographical error in referencing back to those paragraphs in the Example section of the Specification. Text amendments made in the substitute Specification are presented which address and overcome the aforesaid objections without the addition of any new matter. Any additional information which has been included in the substitute Specification and which goes beyond correction of obvious typographical or clerical errors is being incorporated from an information source which was referenced in the original Specification and incorporated therein by reference, or is information which was inherently, if not explicitly, disclosed in the application as originally filed. Specifically, paragraphs 0097 and 0098 (and the corresponding locations in the Appendix II and the sequence listing) have been amended to more directly list certain sequences previously disclosed either inherently but inevitably in the original disclosure (in the case of SEQ ID NO. 24), or disclosed by incorporation by reference to a publication (namely, Efimov *et al.*, FEBS Letters 341:54-58 (1994) for SEQ ID NO. 22 and Genbank database (accession #1705995) for SEQ ID NO. 23) in the original Specification. Such amendments present no new matter to the specification and are otherwise proper in light of the

incorporation by reference of the published data referenced in the original Specification. Withdrawal of the objections to the Specification therefore is respectfully solicited. If any questions remain in this regard, the Examiner is requested to call the undersigned so that the Applicants can understand any concerns the Examiner may have and, if possible, promptly resolve the same.

Claims 1-12, 20 and new claims 24-27 are in the case. New claims 24-27 find support in the Specification at least at paragraphs 0009, 0022, 0050, 0097 and 0098. Claims 13-19 and 21-23 stand withdrawn from consideration due to the requirement now made final by the Examiner. Remaining Claims 1-12 and 20 stand rejected for various reasons detailed below. Each rejection will now be addressed in the order in which they appear in the Office Action.

Section 112 Rejections

Claims 4-5 stand rejected under Section 112, second paragraph. This rejection is respectfully traversed.

Section 112, second paragraph, of the Patent Act, 35 U.S.C. § 112, ¶ 2, requires that the claims of a patent "particularly point [ ] out and distinctly claim[ ] the subject matter which the applicant regards as his invention." In determining indefiniteness of a claim, the question presented is whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. *Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1371, 69 U.S.P.Q.2d 1996 (Fed.Cir.2004). In the present case, both claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In the Office Action, the Examiner asserts, "Claim 4 is indefinite in the recitation of 'wherein the oligomerising domain…is derived from the pentamerisation domain of…COMP' because it is not clear what is meant, *i.e.*, what portion of the oligomerising domain is retained and which portion is not with regard to 'is derived from', and what the actual pentamerisation domain of COMP is given that the instant specification identifies that self assembly of the protein to form pentamers is achieved through the formation of a five stranded helical bundle that involves some 64 N-terminal amino acid residues of the COMP protein and further discloses that the amino acid sequence of the oligomerisation domain has been disclosed by Efimov *et al* which is incorporated by reference." (See Office Action Page 4, fifth paragraph – Page 5, first paragraph). However, one skilled in the art would know what is claimed by the language of

Claim 4 when read in light of the specification. See in this regard the Rule 1.132 Declaration of Gerald T. Nepom submitted herewith. Dr. Nepom is a preeminent scholar in the technical field of the present invention. The Decarlation of Dr. Nepom establishes that a person of ordinary skill in the art at the time the present patent application was filed would have understood what is meant by the phrase "derived from" from Claim 4. In particular, Dr. Nepom notes that a person of ordinary skill in the art would be reasonably apprised of the subject matter being claimed, because such a person would know, within a reasonable level of certainty, whether the oligomerising domain in the second section is derived from the specified domain of COMP through well-known and common techniques, e.g., alignment of amino acid residues. While the language in question may be broad, it is not indefinite under 35 U.S.C. § 112, second paragraph. Thus, Applicants respectfully request the present rejection be reconsidered and withdrawn.

Furthermore, the Specification itself effectively describes the concept of "derived from." The phrase "derived from" is effectively described in paragraph 0050, reading in its last sentence: "Further, similar to the MHC part of the chimeric protein of the invention, this domain can be altered by amino acid substitution, deletion or insertion, as long as the self-assembly of the oligomerising domain is not impaired." The context to this paragraph is also paragraph 0044, especially the second sentence, which reads: "With the term "a functional part thereof" as used herein, a part of a peptide chain is meant, which still exhibits the desired functional characteristics of the full-length peptide it is derived from." See also paragraph [0049] for further context relevant to the phrase in question. Taken as a whole, these teachings and the knowledge which would be possessed by a person of ordinary skill in the art at the time of this invention, as evidenced by Dr. Nepom's declaration, makes clear that the phrase in question is definite for purposes of section 112.

Regarding Claim 5, the Examiner asserts that "Claim 5 is indefinite in the recitation of 'wherein the pentamerisation domain of COMP…comprise and preferably consists of the amino acids 1 to 128, preferably 20 to 83, most preferably 20-72 of COMP' because it is not clear what the metes and scope of the claim are, *i.e.,* which amino acid residues actually are meant." In addition, with regard to the purported indefiniteness of Claim 5, the Examiner asserts, "it is not clear what is meant by 'pentamerisation domain' with regard to the amino acid residues recited in the instant claim because the Efirmov *et al* article incorporated by reference into the instant specification identifies the pentamerization domain of COMP as amino acid residues 20-83 (page

57, column 1, last paragraph of said article and abstract)." (See Office Action, Page 5, first full paragraph). In light of the present amendment to Claim 5, Applicants believe that the section 112 rejection thereof is now moot. One of ordinary skill in the art would know what is claimed by the language of Claim 5, as amended, when read in light of the Specification. Thus, the section 112 rejection of Claim 5 should be reconsidered and withdrawn.

Section 102(e) Rejection No. 1

Claims 1-3, 6-12, and 20 stand rejected as anticipated under Section 102(e) by US 2005/0003431 A1 (Wucherpfenning, et al.). . This rejection is respectfully traversed.

To establish a *prima facie* case of anticipation, an examiner has the burden of making a *prima facie* showing that the cited reference reveals all of the elements of the claimed invention, either explicitly or inherently, so as to prove the claimed invention's existence in the prior art. *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997). To prove the claimed invention's existence in the prior art, the Examiner cannot read into the prior art teachings that are not there. *Id.* As to the requirements for establishing a prima facie case of anticipation, *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458, 221 USPQ 481, 485 (Fed. Cir. 1984) (*citing Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983)) points out:

> Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim.

Because all features of the presently rejected claims are not taught by the cited reference cited, the Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of anticipation for Claims 1-3, 6-12, and 20.

It is suggested in Wucherpfenning, et al. that the transmembrane portion of Class II MHC complexes in particular stabilizes the folding of the alpha and beta chains in these complexes, and that these alpha and beta chains are aligned at a certain position due to their membrane bound nature. Making soluble recombinant Class II MHC complexes, *i.e.* with the transmembrane domain deleted has been difficult, since the alpha and beta chains do not refold very well with one another. When these chains are truncated for soluble recombinant expression the natural alignment of the protein chains at the cell membrane is missing, leading to low yield and stability of the complexes.

In the prior art, including in Wucherpfenning, et al, it has therefore been suggested to facilitate the formation of these recombinant monomeric Class II MHC complexes by constructing fusion proteins that include, e.g. at the C-termini of the alpha and beta chains, complementary versions of other protein molecules that also form heterodimers, that dimerise with high affinity and complementarity. An example, which is given in Wucherpfenning, et al, is to use heterodimeric leucine zipper molecules derived from the Fos and Jun proteins, which are coiled-coil proteins. As a consequence, Wucherpfenning, et al describes an improved method of using these heterodimeric coiled-coil protein sub-units to form Class II MHC complex monomers, *i.e.* as heterodimers of their alpha and beta chain subunits.

In contrast, the present invention describes MHC proteins fused to the oligomerisation domain of coiled-coil proteins to form MHC complex multimers. Claim 1 of the present application includes the feature "…wherein formation of the oligomeric MHC complex occurs by oligomerisation at the oligomerising domain of the chimeric proteins and wherein at least two of the first sections are derived from the same MHC peptide chain". This means that the resulting MHC complex formed by oligomerisation at the coiled-coil domains will be a multimer comprising at least two identical MHC peptide chains. Wucherpfenning, et al. does not describe the use of oligomerisation at the oligomerising domains of coiled-coil proteins to generate MHC complex oligomers in general and does not describe the above feature of the present Claim 1, in particular. The reason for this is that the objective of Wucherpfenning, et al. was to facilitate the formation of heterodimeric MHC class II complex monomers, rather than MHC complex multimers. Where the formation of MHC complex multimers was required by Wucherpfenning, et al., this was achieved by other means, such as labeling of the MHC complexes with biotin and subsequent coupling to streptavidin, in the present invention.

The oligomeric MHC complex of the present invention in fact overcomes the disadvantages and drawbacks of Wucherpfenning, et al. Oligomeric MHC complex can have a substantially higher affinity to a T cell receptor than an oligomer obtained by *e.g.* tetramerising the MHC complexes by coupling through biotin and streptavidin. It is believed that this increase in affinity is achieved when three or more MHC molecules are arranged substantially in the same plane with all binding faces oriented in the same direction. In contrast, because the tetrameric streptavidin-coupled complex in Wucherpfenning, et al. has a tetrahedral arrangement, at best only three MHC binding domains are available simultaneously for contacting the T cell surface.

Because the Wucherpfenning, et al. reference has failed to actually teach that which it is asserted to anticipate, the Examiner has failed to establish a *prima facie* case of anticipation as to Claims 1-3, 6-12, and 20, and the rejection should be withdrawn.

Section 103(a) Rejections

Claims 1, 4, 5, and 20 stand rejected as obvious under Section 103(a) over US2005/0003431 (Wucherpfenning, *et al.*) in view of Terskikh *et al.* (PNAS USA 1997, 94:1663-1668, IDS reference), Muller *et al.* (Meth. Enzymol. 2000, 326, pages 261-282, IDS reference), Efimov *et al.* (FEBS Letters, 1994, 341: 54-48) and Efimov *et al.* (Proteins 1996, 24:259-262). This rejection is respectfully traversed.

As the United States Supreme Court has very recently stated, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. ___, 127 S.Ct. 1727, 1741, 82 U.S.P.Q.2d 1385 (April 30, 2007) (citing *United States v. Adams*, 383 U.S. 39, 40, 86 S.Ct. 708, 15 L.Ed.2d 572 (1966)). Post-*KSR*, an Examiner is still required, as has always been the case, to "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* This still must be established without the use of hindsight reasoning having the benefit of Applicants' disclosure.

The Examiner has failed to meet her burden in the present case because a person of ordinary skill in the art at the time of the present invention would not have had a legitimate, apparent reason to combine the teachings of the cited references to arrive at the present invention. First, the defects in the disclosure of US2005/0003431 noted above as relates to disclosing the invention of Claim 1 and claims depending therefrom are reiterated here by reference. In addition, the accompanying Rule 1.132 Declaration of Gerald T. Nepom (the "Declaration") is submitted in support of Applicants' traversal of this rejection. In particular, Dr. Nepom, having reviewed all of the cited prior art, indicates that a person of ordinary skill in the art, at the time this patent application was filed in the United States, would not have been motivated to combine the cited references to achieve the particular invention of Claim 1 and the claims depending therefrom. (Declaration, paragraphs 4-6.) As Dr. Nepom points out, the Terskikh *et al.* reference actually teach away from the presently claimed invention, in that it

discourages multimerization using larger molecules such as Fv fragments, not to mention even larger MHC complexes. (See Terskikh *et al.* at page 1668, lines 31-35.) As Dr. Nepom further explains, IgM pentamer structures discussed in Terskikh *et al.* also would not have suggested or made apparent the presently claimed invention, because of person of ordinary skill in the art would have understood the significant differences between an IgM pentamer scaffold and a coiled-coil protein, since the Ig variable domains are structurally similar in size and orientation to the MHC domains which are used in the multimers. (Declaration, paragraph 5.) Such a change in scaffold to the coiled-coil protein would not have been obvious to the person of ordinary skill in the art at the time of the present invention. (*Id.*)

As Dr. Nepom further notes, there were a large number of biochemical and structural reasons why a person of ordinary skill in the art at the filing date of this application would not have found obvious the use of the coiled-coil proteins of the invention as a scaffold to multimerise MHC molecules. These include issues of protein solubility, stereochemistry, steric inhibition with function and folding, misfolding of the macromolecular ligand, and orientation of the assembled complex. There simply was no way, *a priori*, to predict that these significant issues would actually be able to accommodate the MHC peptide structure as ligand attached to a portion of the coiled-coil protein. Nor would there have been any motivation, from the cited literature or from the body of common knowledge, for a person of ordinary skill at the relevant time to attempt such a combination with any reasonable expectation of success. (Declaration, paragraph 6.)

Neither Muller *et al.* nor the other cited references relied upon by the Examiner supply a disclosure of multimers of the same MHC peptide chain. Moreover, Muller *et al.* relies upon Terskikh *et al.* for its teachings with respect to the use of COMP as a multimerization fusion partner. (See Muller et al. at page 273, last table entry and ref. 53.) Simply put, with a fair and complete reading of the cited references, there is no support for the assertion that a person of ordinary skill in the art, at the time the present invention was made, would have found it apparent to use the coiled-coil proteins of the invention as a scaffold to multimerise MHC molecules. Accordingly, the cited references cannot support a *prima facie* case of obviousness, and the rejection of Claims 1, 4, 5, and 20 under Section 103(a) should be reconsidered and withdrawn.

Provisional Non-statutory Obviousness-type Double Patenting Rejection

Claims 1-12 and 20 stand provisionally rejected over commonly assigned patent application 10/770,140 on the basis of obviousness-type double patenting. This rejection is respectfully traversed. Applicants do not at this time concede that the claims of the respective applications are patentably indistinct. However, it should be noted that the present application and application number 10/770,140 were both filed in the U.S. on the same day, i.e., February 2, 2004. Since the applications were co-filed, the present application should be considered the base application for co-filed patent applications in accordance with MPEP § 804(I)(B)(1). This rejection should therefore be withdrawn to allow the present application to issue without any requirement for a terminal disclaimer.

Section 102(e) Rejection No. 2

Claims 1-12 and 20 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by commonly assigned patent application publication US 2005/0074848 A1. The effective date of the cited reference is February 2, 2004, the same date as the U.S. filing date for the present application. Accordingly, the cited reference US 2005/0074848 A1 is not section 102(e) prior art with respect to the present claims, since it was not published "before" Applicants' constructive date of invention (which is at least as early as February 2, 2004). Accordingly, this rejection is without merit and should be withdrawn.

In view of all of the foregoing, the pending Claims 1-12, 20 and 24-29 are believed to be in a condition for allowance. Notification to this effect would be sincerely appreciated.

Respectfully submitted,

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